# Impact of regulatory proteins on the nonlinear dynamics of DNA

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In this paper we examine the nonlinear dynamics of a DNA chain whose exciton modes are affected by regulatory proteins that may become bound to the DNA chain by hydrogen bonds. The dynamics of the DNA chain is described by the Peyrard-Bishop model. Since this model gives rise to large-amplitude broad oscillations of base pairs, we consider the impact of attached regulatory proteins on the so-called breathers or bubbles. Assuming that an ideal gas of bubbles may exist in the DNA chain at physiological temperatures we adopt a statistical approach to calculate the average size of base-pair stretching under the prevailing conditions.

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## I. INTRODUCTION

Deoxyribonucleic acid (DNA) is doubtlessly the most important biomolecule. Its double stranded helical structure undergoes a very complex dynamics and the knowledge of that dynamics provides insights into various related biological phenomena, such as transcription, translation, and mutations. The key problem in DNA biophysics is how to relate functional properties of the DNA with its structural and physical dynamical characteristics. In this paper our aim is to establish a plausible relationship between the regulation of transcription processes and the nonlinear dynamics of DNA.

The possibility that nonlinear effects might concentrate the vibrational energy of DNA into localized solitonlike objects was first contemplated by Englander *et al.* [1]. Although several authors [2–9] have suggested that either topological kink solitons or bell-shaped breathers would be good candidates to play a basic role in the DNA nonlinear dynamics, there are still several unresolved questions in this regard. The hierarchy of the most important models for nonlinear DNA dynamics was presented by Yakushevich [10].

In the present paper we have strongly relied on the extended model for DNA dynamics, first proposed by Peyrard and Bishop [7]. In the following, we first outline the main features of that model, which will be henceforth referred to as the PB model for short. In that context we have examined in detail the necessary conditions for the existence of breather excitations in DNA chains. We then focus our attention on the very important biophysical situation where the breather solution of the PB model is suspected of playing the role of a conformational agent in the process of gene expression. In that respect, the impact of regulatory proteins on breather dynamics was examined by the method of nonequilibrium statistical physics allowing the calculation of an average stretching distance of the base pairs involved.

The present paper is organized in the following way. In Sec. II, for clarity and conciseness we outline the PB model primarily proposed to describe the process of local opening of DNA base pairs (or local melting of the double helix). Then we have attempted to shed more light on the still somewhat vague parameter values of the PB model. This is important in the determination of the necessary conditions for the existence of breather solitons. In Sec. III, we present one class of specific regulatory proteins, which are attached by hydrogen bonds to a DNA chain. We conjecture that these proteins, possessing a well-known carbon oxide stretching mode could resonantly impact on the DNA dynamics increasing the magnitude of stretching base pairs involved in the breather's dynamics. In Sec. IV we present a discussion and conclusions regarding the feasibility of this approach in explaining the role of regulatory proteins in controlling gene expression.

## II. THE PHYSICAL CONCEPT OF THE PB MODEL IN DNA

The *B*-form DNA in the Watson-Crick model [11] is a double helix consisting of two strands $B_1$ and $B_2$ (see Fig. 1) with the characteristic dimensions depicted. Molecular masses of nucleotides (considered without adjacent sugar groups) range from 340 (cytosine) to 380 mu (guanine). Therefore, it is apparent that the four constituent base nucleotides (adenine, cytosine, guanine, and thymine) do not differ in their mass by more than 13%, thus inhomogenities due to the base sequences are usually ignored in biophysical models of DNA dynamics.

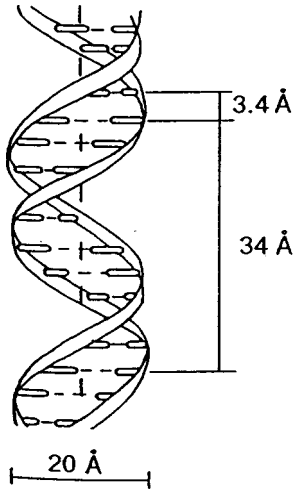


FIG. 1. Sketch of the double helix. The sugar-phosphate backbone is shown as ribbons. The bases are depicted as short transverse rods.

 

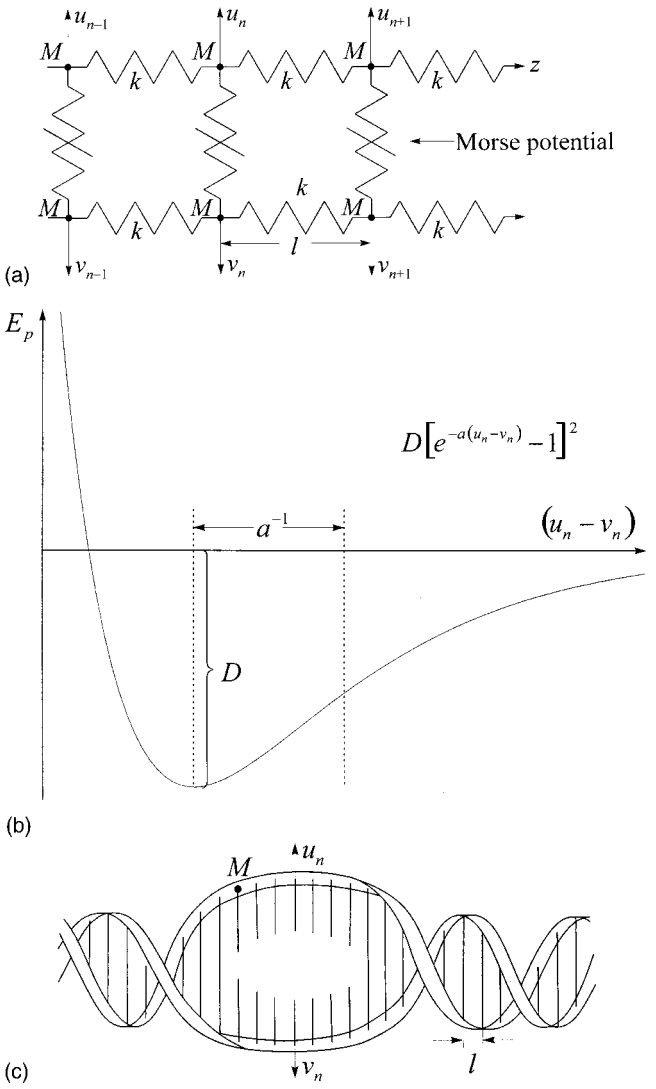


FIG. 2. (a) Schematic representation of the displacements in the DNA lattice; (b) the corresponding Morse potential between base pairs; and (c) a bubble defect.

Consequently, a common mass $M$ is used for the bases, and the same coupling constant $k$ for the nearest-neighbor harmonic interactions along each strand is assumed, see Fig. 2(a).

The strands are coupled to each other through hydrogen bonds that are supposed to be responsible for transverse displacements of base pairs. According to the rule of Chargaff and co-workers [12] there are only two types of base pairs in DNA; *A-T* and *G-C* pair, see Fig. 3. An *A-T* pair is linked by two, while *G-C* pair consists of three hydrogen bonds. Hence, hydrogen bond variability in DNA exhibits a more conspicuous inhomogenity than the corresponding mass distribution.

Nonetheless, this inhomogenity is neglected in the PB model and the hydrogen bond interactions are averaged out and modeled by the Morse potential [see Fig. 2(b)]. The three-dimensional helicoidal structure of the DNA chain implies that neighboring base nucleotides from different strands are sufficiently close to interact through water filaments. This

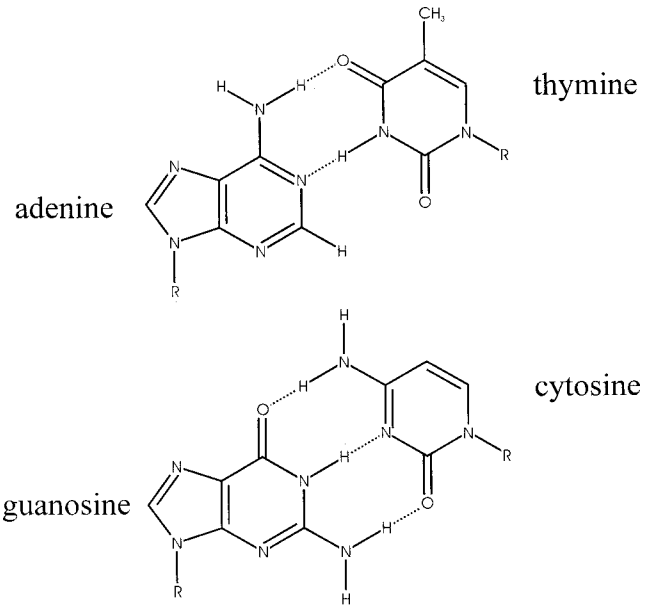


FIG. 3. Base pairs: (a) *A-T* and (b) G-C. Hydrogen atoms that are substituted in DNA for carbon atoms of sugar rings are marked by asterisks.

means that a base at the site $n$ of one strand, interacts with both the $(n+4)$th and the $(n-4)$th bases of the other strand. Introducing the transverse displacements $u_n$, $v_n$, of the bases from their equilibrium positions along the direction of hydrogen bonds the PB Hamiltonian [13] for the DNA chain is given in the form

$$H_{\mathrm{PB}}=\sum_n \left(\left(\frac{P_{n1}^2}{2M}+\frac{P_{n2}^2}{2M}\right)+\tfrac{1}{2}k[(u_n-u_{n-1})^2+(v_n-v_{n-1})^2] +\tfrac{1}{2}K[(u_n-v_{n+4})^2+(u_n-v_{n-4})^2] +D\{\exp[-a(u_n-v_n)]-1\}^2\right). \tag{2.1}$$

As already mentioned, $M$ stands for the mass of a base nucleotide, $P_{n1}=Mu_n$ and $P_{n2}=Mv_n$ are the base momenta, $k$ (or $K$) is the harmonic elastic constant of the longitudinal (or helicoidal) springs. Finally, $D$ and $a$ are the depth and the inverse width of the Morse potential well, respectively [see Fig. 2(b)].

It is more convenient to describe the transversal motion of the two DNA strands in terms of the center-of-mass coordinates representing the in-phase and out-of-phase transversal motions

$$x_n=\frac{1}{\sqrt{2}}(u_n+v_n); \quad y_n=\frac{1}{\sqrt{2}}(u_n-v_n). \tag{2.2}$$

The dynamical equations of motion derived from the Hamiltonian (2.1) are then

$$M\ddot{x}_n=k(x_{n+1}+x_{n-1}-2x_n)+K(x_{n+4}+x_{n-4}-2x_n)+\cdots \tag{2.3}$$

$$M\ddot{y}_n = k(y_{n+1}+y_{n-1}-2y_n) - K(y_{n+4}+y_{n-4}+2y_n) + 2\sqrt{2}aD(e^{-a\sqrt{2}y_n}-1)e^{-a\sqrt{2}y_n}. \quad (2.4)$$

Equation (2.3) describes the well-studied linear waves (phonons) while Eq. (2.4) yields nonlinear solitonlike breathers. Consequently, we pay close attention to the nonlinear Eq. (2.4) bearing in mind that a stable breather solution may be viewed as a candidate for long-range interactions along DNA chains.

According to the original approach of Ref. [13] it is assumed that the oscillations of bases are large enough to be anharmonic, but still insufficient to break the bond since the plateau of the Morse potential is not yet reached. Thus, it is presumed that the base nucleotides oscillate around the bottom of the Morse potential allowing the following transformation to be safely implemented:

$$y_n = \epsilon\Phi_n; \quad \epsilon \ll 1. \quad (2.5)$$

Equation (2.4) can now be expanded to fourth order terms in $\epsilon$, resulting in the following form:

$$\ddot{\Phi}_n = \frac{k}{M}(\Phi_{n+1}+\Phi_{n-1}-2\Phi_n) - \frac{K}{M}(\Phi_{n+4}+\Phi_{n-4}+2\Phi_n) - \omega_q^2(\Phi_n+\epsilon\alpha\Phi_n^2+\epsilon^2\beta\Phi_n^3)-\cdots, \quad (2.6)$$

where the new notation is introduced as

$$\omega_q^2 = \frac{4a^2D}{M}, \quad \alpha = -\frac{3a}{\sqrt{2}}, \quad \beta = \frac{7a^2}{3}. \quad (2.7)$$

Note that Eq. (2.6) possesses two time scales. The first one corresponds to the vibrations of the nucleotide around its equilibrium position and the second, much larger, to the propagation of a collective coherent structure along the DNA chain. Therefore, one can safely apply the reductive perturbation method expanding in the small parameter $\epsilon$ and using a semidiscrete approximation [14];

$$\Phi_n(t) = F_1(\epsilon n\ell,\epsilon t)e^{i\Theta n} + \epsilon\{F_0(\epsilon n\ell,\epsilon t) + [F_2(\epsilon n\ell,\epsilon t)]e^{i2\Theta n}\} + \text{c.c.} + \Theta(\epsilon^2)$$

and

$$\Theta_n = nq\ell - \omega t. \quad (2.8)$$

Here, $\omega$ represents the optical frequency of the base-pair vibrations, $\ell$ is the distance between neighboring bases in the same strand, and $q$ is the wave number whose role will be discussed later.

Now we consider a continuum limit via a multiple-scale expansion, where

$$Z = \epsilon z; \quad T = \epsilon t. \quad (2.9)$$

This means that the nonlinear excitation that emerges in this picture consists of a carrier wave modulated by a slowly varying envelope. The expansion Eq. (2.8) together with the scaling in Eq. (2.9) yield the following continuum approximation transformations:

$$F(n\pm1)\to F(Z,T)\pm F_Z(Z,T)\epsilon\ell + \tfrac{1}{2}F_{ZZ}(Z,T)\epsilon^2\ell^2$$

$$F(n\pm4)\to F(Z,T)\pm F_Z 4\epsilon\ell + \tfrac{1}{2}F_{ZZ}(Z,T)16\epsilon^2\ell^2$$

and

$$\ddot{\Phi}_n \to (\epsilon^2F_{1TT} - 2i\epsilon\omega F_{1T} - \omega^2F_1)e^{i\Theta} + \epsilon^2F_{0TT} + (\epsilon^3F_{2TT} - 4i\epsilon^2\omega F_{2T} - 4\epsilon\omega^2F_2)\epsilon^{i2\Theta} + \text{c.c.}, \quad (2.10)$$

where $F_Z$ and $F_T$ stand for the corresponding derivatives with respect to the new variables $Z$ and $T$, etc. Following a rather tedious algebra, we obtain a set of important relations from Eq. (2.6). Equating the coefficients for the first harmonic ($e^{i\Theta n}$) one obtains

$$\epsilon^2F_{1TT} - 2i\epsilon\omega F_{1T} - \omega^2F_1 = \frac{k}{M}\{2F_1[\cos(q\ell)-1] + 2i\epsilon\not{\ell}F_{1Z}\sin(q\ell) + \epsilon^2\not{\ell}^2F_{1ZZ}\cos(q\ell)\} - \frac{K}{M}\{2F_1[\cos(4q\ell)+1] + 4i\epsilon\ell F_{12}\sin(4q\ell) + 16\epsilon^2\ell^2F_{1ZZ}\cos(4q\ell)\} - \omega_q^2[F_1 + \epsilon^2(2\alpha F_0F_1 + 2\alpha F_1^*F_2 + 3\beta|F_1|^2F_1)]. \quad (2.11)$$

After neglecting all the terms with $\epsilon$ in Eq. (2.11), a dispersion relation is found to be in the following form:

$$\omega^2 = \omega_g^2 - \frac{2k}{M}[\cos(q\ell)-1] + \frac{2K}{M}[\cos(4q\ell)+1]. \quad (2.12)$$

From Eq. (2.12) one obtains the group velocity for the wave packet as

$$V_g = \frac{\ell}{M\omega}[k\sin(q\ell) - 4K\sin(4q\ell)]. \quad (2.13)$$

Equating the coefficients for $e^{i\Theta n}$ and $e^{i3\Theta n}$ we link the functions $F_0$, $F_1$, and $F_2$ as follows:

$$F_0 = \mu|F_1|^2; \quad F_2 = \delta F_1^2, \quad (2.14)$$

where

$$\mu = -\frac{2\alpha}{\left(1+\frac{4K}{M\omega_g^2}\right)}; \quad \delta = -\frac{\beta}{2\alpha}. \quad (2.15)$$

Thus, taking into account Eq. (2.14), then again introducing new independent variables

$$S = Z - V_g T, \quad \tau = \epsilon T, \tag{2.16}$$

and equating coefficients with $\epsilon^2$ in Eq. (2.11), one obtains a nonlinear Schrödinger equation (NSE) for the leading term $F_1$ in the expansion, Eq. (2.8),

$$iF_{1\tau} + PF_{1SS} + Q|F_1|^2 F_1 = 0. \tag{2.17}$$

Here, the dispersion coefficient $P$ and the parameter of nonlinearity $Q$ are explicitly given by

$$P = \frac{1}{2\omega}\left\{\frac{\ell^2}{M}[k\cos(q\ell) - 16K^2\cos(4q\ell)] - V_g^2\right\} \tag{2.18}$$

and

$$Q = -\frac{\omega_g^2}{2\omega}[2\alpha(\mu+\delta) + 3\beta].$$

It is important to note that provided $PQ>0$, Eq. (2.17) exhibits an envelope-soliton solution called a breather (or a bubble), which is expressed as

$$F_1(S,\tau) = A\,\mathrm{sech}\left[\frac{S-u_e\tau}{L_e}\right]\exp\left[\frac{iu_e(S-u_e\tau)}{2P}\right]\cdots, \tag{2.19}$$

where the envelope amplitude $A$ and its width $L_e$ are expressed as follows:

$$A = \frac{(u_e^2 - 2u_e u_c)^{1/2}}{2PQ}; \quad L_e = \frac{2P}{(u_e^2 - 2u_e u_c)^{1/2}} \tag{2.20}$$

with $u_e$ and $u_c$ being the velocities of the envelope and the carrier wave, respectively. Subsequently, by setting

$$V_e = V_g + \epsilon u_e; \quad \Theta = q + \frac{\epsilon u_e}{2P};$$

$$\Omega = \omega + \frac{\epsilon u_e}{2P}(V_q + \epsilon u_c)\cdots, \tag{2.21}$$

Eqs. (2.19), (2.8), (2.9), and (2.14) can be transformed to give a final form of the breather function as

$$\Phi_n(t) = 2A\,\mathrm{sech}\left[\frac{\epsilon}{L_e}(n\ell - V_e t)\right]\cos(\Theta n\ell - \Omega t) + \epsilon A\,\mathrm{sech}\left[\frac{\epsilon}{L_e}(n\ell - V_e t)\right] \times\left[\frac{\mu}{2} + \delta\cos 2(\Theta n\ell - \Omega t)\right]. \tag{2.22}$$

In order to demonstrate that the condition for the existence of a breather $PQ>0$ is satisfied we now attempt to make a careful numerical estimate. Before we do that, however, it must be born in mind that the values of the parameters involved in the PB model are still somewhat controversial. For example, by direct measurements of the interactions between bases of *A*-*T* pairs using a surface force apparatus [15] it was revealed that the range of the *A*-*T* forces in water is as large as 38 nm and it does not resemble any known surface force. It has also been shown that a small chemical change can noticeably modulate the interactions. As our initial choice we adopt the set of parameter values ascribed to DNA in Ref. [13], reserving the right to a reevaluation of this choice at a later stage. The selected numbers are

$$k = 24\ \mathrm{N/m}, \quad a = 2\times 10^{10}\ \mathrm{m}^{-1},$$

$$K = 8\ \mathrm{N/m}, \quad D = 0.1\ \mathrm{eV},$$

$$l = 3.4\times 10^{-10}\ \mathrm{m}, \quad u_e = 10^5\ \mathrm{m/J}$$

and

$$M = 5.4\times 10^{-25}\ \mathrm{kg}, \quad u_c \approx 0. \tag{2.23}$$

As a result, we are able to estimate the parameters involved in the nonlinearity parameter $Q$:

$$\mu = \frac{4a\sqrt{2}}{3} = 3.8\times 10^{10}\ \mathrm{m}^{-1}; \quad \delta = \frac{7a\sqrt{2}}{18} \approx 1.1\times 10^{10}\ \mathrm{m}^{-1}. \tag{2.24}$$

Thus using Eqs. (2.7) and (2.18) we can infer that the inequality $Q>0$ holds.

From Eq. (2.20) we see that the inequality $L_e>0$ follows if both $u_e>2u_c$ and $P>0$ hold. This implies that we must have $A>0$, which can in fact be inferred from Eq. (2.20). Otherwise, the breather soliton could not exist. In summary, we expect that on the basis of the above choice of the model parameters the breather soliton should exist in the DNA chain given the conditions in the PB model. Otherwise, based on the measurements reported in Ref. [15] we readily conclude that the parameter $a$ should have a value at least two orders of magnitude smaller. Nevertheless the condition $Q>0$ still holds, but it remarkably lowers the value of the nonlinearity parameter $Q$. The outcome of this would be that the nonlinear term in NSE, Eq. (2.17), could not be competitive with the dispersive term, thus preventing the existence of breather solitons. Since the method used in the measurement of the forces between base pairs [15] was not applied to DNA itself but to some two-dimensional Blodgett films of *A*-*T* pairs, it is still possible that such a large decrease in the value of the parameter $a$ is a result of the effect of collective action of hydrogen bonds. Consequently, there is still an element of uncertainty remaining in the choice of the parameter values.

We now wish to discuss some of the breather features in the context of the dispersion parameter $P$. It should be noticed from Eq. (2.18) that this parameter does not depend on any of the uncertain values ($a$, $D$).

In Figs. 4 and 5, the group velocity $V_g$ and the dispersion coefficient $P$ are depicted versus $q\ell$, according to Eqs. (2.13) and (2.18), respectively. The frequency $\omega$ was calculated from the dispersion relation given by Eq. (2.12). For $V_g>0$ and $P>0$, several multiples of $q\ell$ are allowed thus favoring the existence of a breather. The intuition gained in studying nonlinear systems in condensed matter physics fa-

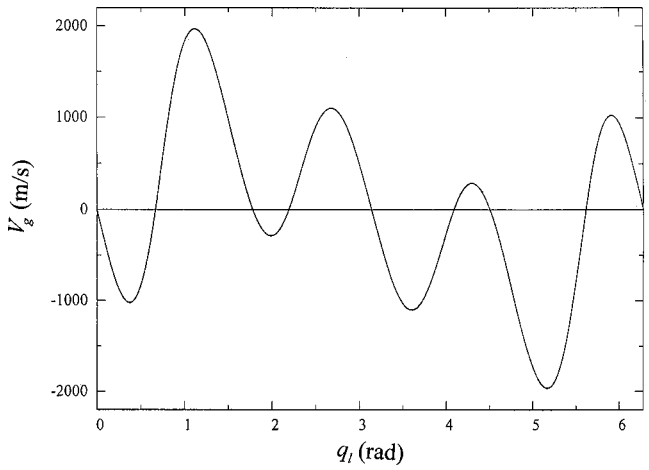


FIG. 4. Plot of the group velocity $V_g$ as a function of $q\ell$ according to Eq. (2.18).

vors the conclusion that the wavelength $\lambda$ of the lattice carrier wave ($q=2\pi/\lambda$) should be an integer multiple of lattice spacing $\ell$. Thus the following four options are possible:

$$\lambda_1=6\ell, \quad (q\ell=1.05 \text{ rad});$$

$$\lambda_2=7\ell, \quad (q\ell=0.90 \text{ rad});$$

$$\lambda_3=8\ell, \quad (q\ell=0.78 \text{ rad});$$

$$\lambda_4=9\ell, \quad (q\ell=0.70 \text{ rad}). \tag{2.25}$$

All these four values lie in the first allowed ''zone'' for $\lambda$, $(5.7\ell<\lambda<9.5\ell)$, or equivalently $(0.66<q\ell<1.11)$. It is natural to expect that other allowed zones do not contain any $\lambda$ as integer multiples of $\ell$. For example, the second zone reads $(2.3\ell<\lambda<2.9\ell)$.

It is instructive to plot the function $\Phi_n(t)$, given by Eq. (2.22). We choose $n=300$ and $\omega$ given by Eq. (2.12). In Fig. 6 we selected $q\ell=0.78$ rad while in Fig. 7 $q\ell=1.05$ rad.

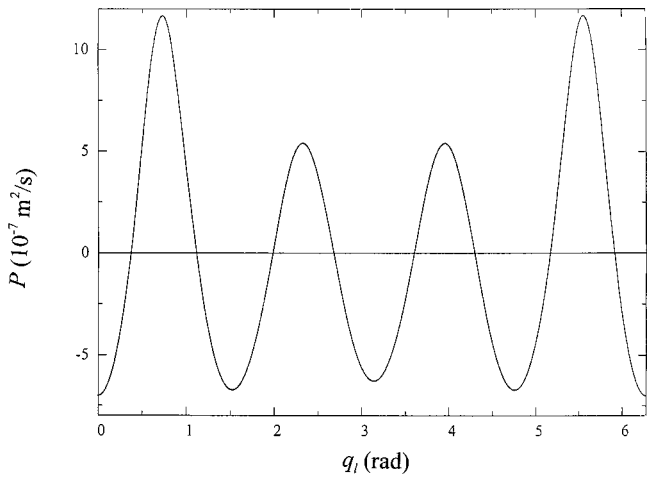


FIG. 5. Plot of the dispersion parameter $P$ as a function of $q\ell$ according to Eq. (2.18).

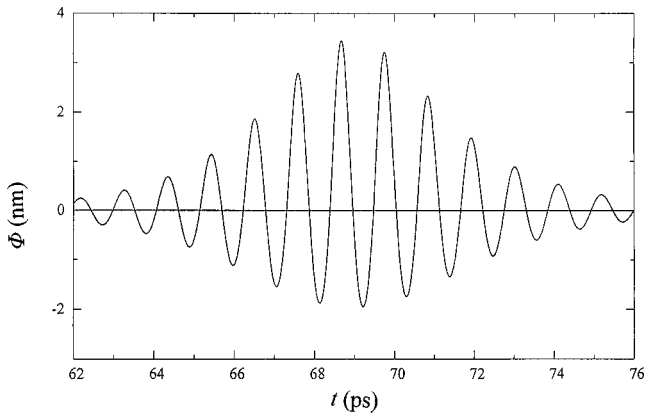


FIG. 6. Plot of the function $\Phi_n(t)$ given by Eq. (2.22) for $q\ell=0.78$ rad.

The figures show typical breatherlike shapes indicating that the choice $q\ell=0.78$ rad represents a more compact conformational excitation.

## III. THE STATISTICAL MODEL OF A REGULATORY PROTEIN-DNA INTERACTION

The idea of transmission of regulatory signals came from the results of experiments in which the so-called long-range effects were studied in DNA. To describe this effect, let us consider a simple system consisting of two protein molecules and one DNA molecule, (Fig. 8). It is assumed that the first regulatory protein molecule can bind (with good efficiency—via the lock-and-key mechanism) to a special segment of the DNA molecule. Let it be called site 1. It is also assumed that the other protein molecule is bound to the DNA at another site called 2. Numerous experimental data [16,17] show that the first protein bound at site 1 influences the interaction of the second protein molecule with DNA at site 2. Furthermore, the distance between the sites can reach hundreds or even thousands of base pairs.

To explain this effect many alternative models of the action at a long distance have been proposed [18,19]. Our pre-

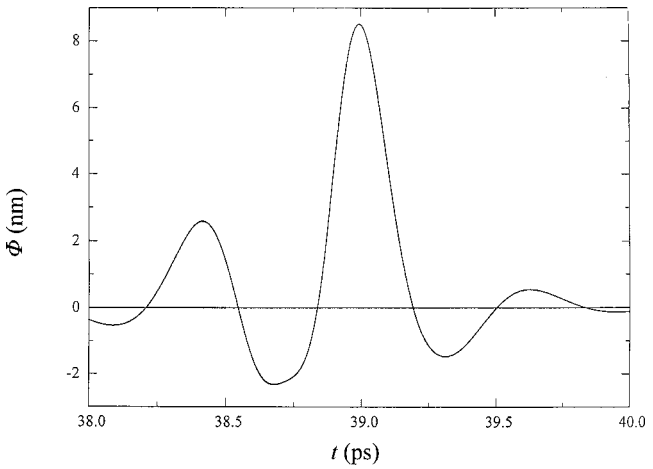


FIG. 7. Plot of the function $\Phi_n(t)$ given by Eq. (2.22) for $q\ell=1.05$ rad.

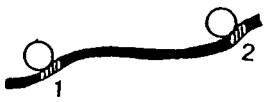


FIG. 8. A schematic representation of the DNA molecule interacting with two protein molecules. The DNA molecule is represented by a black band; the sites interacting with proteins are shaded; protein molecules are represented by small circles.

ferred assumption is that binding of the first protein molecule produces a mode of energy that is accompanied by a local conformational distortion of base pairs causing a breather excitation or enhancing the amplitude of an already existing breather excitation. Such a breather propagates along the DNA chain, and upon reaching site 2 it changes the conformational state of the site, which in turn changes the binding constants of the second protein with the DNA chain.

Specific interactions of regulatory proteins with DNA are usually defined through hydrogen bonding interactions between functional groups of amino acid side chains or the peptide bonds and groups of the bases in the major or minor grooves of the DNA chain. Here, we restrict our consideration to those regulatory proteins with hydrogen bonds to the DNA. Figure 9 represents the protein glutamine bound by two hydrogen bridges to an *A-T* base pair in the major groove [20].

We recall that every protein has a peptide group, which contains a double-bonded carbon-oxygen complex (or amide-I bond) with a characteristic quantum of energy of 0.205 eV (corresponding to a peak at 1650 $cm^{-1}$). The amide-I bond appears to be of great interest here as a potential ''basket'' for storage and transport of biological energy. This part of glutamine protein is indicated in Fig. 9 by an ellipse. The amide-I exciton mode was prominently exposed in the theory of Davydov molecular solitons that was also applied to $\alpha$-helical chains [21,22]. However, a problem arises when we note that in a single peptide group, the lifetime of an amide-I vibration is of the order of $10^{-12}$ s [22]. We conjecture that the energy of this mode could be utilized in producing a conformational change in a neighboring base pair (*A-T*) that is mediated by hydrogen bonds depicted by a rectangle in Fig. 9. Below we elaborate on the quantitative description of such a model.

Let us first introduce the extended Hamiltonian in an attempt to model the above regulatory process in DNA. The Hamiltonian should consist of two parts as follows:

$$H = H_0 + H_{\rm int}, \tag{3.1}$$

where the Hamiltonian $H_0$ consists of two terms, first of which represents the part of the PB Hamiltonian (2.1) containing the separated coordinates $y_n$ and momenta $P_{yn} = M\dot{y}_n$, while the second one corresponds to the amide-I mode in the regulatory protein, considered here. Hence,

$$H_0 = H_y + H_{C=0}, \tag{3.2}$$

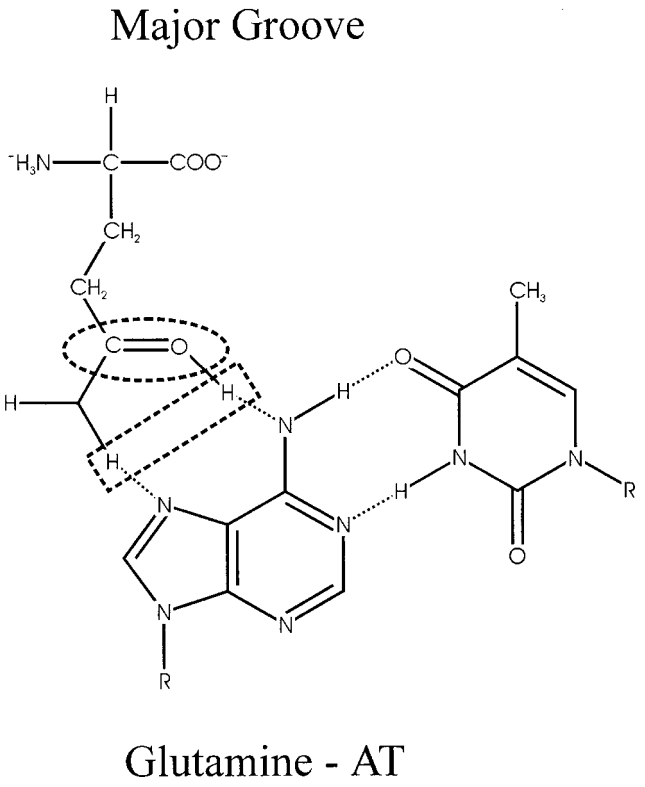


FIG. 9. Protein-DNA hydrogen bonding. The structure of a *C-G* base pair bound to arginine is shown following Ref. [20] in which the guanidinium group of arginine binds to the N7 and 06 positions of guanine. Glutamine can hydrogen bond specifically to the adenine, whereas the carbonyl oxygen group binds to the N6 position of adenine. A specific amino-acid–base-pair hydrogen bond can be made in a minor groove between asparagine and a *G-C* base pair. Asparagine binds with the terminal amino group to the N3 position of guanine, whereas the carbonyl oxygen hydrogen bonds to the N2 position of guanine.

$$H_y = \sum_n \left\{ \frac{P_{yn}^2}{2M} + \frac{k}{2}(y_n - y_{n-1})^2 + \frac{K}{2}[(y_n - y_{n-4})^2 + (y_n - y_{n+4})^2] + D(e^{-\sqrt{2}ay_n} - 1)^2 \right\}, \tag{3.3}$$

and

$$H_{C=0} = E_\kappa C_\kappa^+ C_\kappa, \quad E_\kappa = 0.205 \text{ eV}, \tag{3.4}$$

where $E_\kappa$ is the energy of the amide-I mode, while $C_\kappa^+$, $C_\kappa$ represent the creation and annihilation operators, respectively, of an excited state possessing the wave vector $\kappa$.

Finally, $H_{\rm int}$ describes the interaction between the amide-I mode and the nearest base pairs of DNA. It could be conveniently written in the form

$$H_{\rm int} = \sum_m H_{\rm int}^{\rm op} f_m(t), \tag{3.5}$$

where the operator part of the interaction is given as follows:

$$H_{\rm int}^{\rm op}=(C_\kappa+C_\kappa^+)y_m, \tag{3.6}$$

while the Heaviside-type interaction switching function has the form

$$f_m(t)=V_m e^{-\sigma^2(m-\ell)^2}\{\theta(t-\tilde{\tau}(m-1))-\theta(t-\tilde{\tau}(m+1))\}. \tag{3.7}$$

Since we already used $\tau$ for a variable in Eqs. (2.16)–(2.19) we now use a modified symbol $\tilde{\tau}$ in order to avoid confusion. We assumed here that due to its hydrogen character, the interaction term drops exponentially with distance from its original magnitude $V_m$. It is also assumed here that the protein molecule is located at site $\ell$ of the DNA chain. The Fourier transform of the time-dependent part of the interation in Eq. (3.7)

$$f_m(t)=\frac{1}{2\bar{u}}\int_{-\infty}^{+\infty}d\omega e^{-i\omega t}f_m(\omega)$$

yields

$$f_m(\omega)=2V_m e^{-\sigma^2(m-\ell)^2}\left[\frac{\sin(\tilde{\tau}\omega)}{\omega}\right]e^{i\omega\tilde{\tau}m}. \tag{3.8}$$

Since the breather solitons in DNA can be generated in different ways, various causes that have been suggested include the thermal fluctuations as well as local ligand-protein interactions considered here, in addition to the chemical energy released during ATP hydrolysis. It is apparent to us that in a very long DNA chain an ideal gas of breathers can be generated via one or several of these mechanisms. Consequently, we need to develop a statistical approach in order to compute the average value of the base-pair displacement resulting in the process. For this purpose we use the well-known method of nonequilibrium statistical mechanics developed by Zubarev [23] according to which the average value of an arbitrary physical operator $\hat{A}$ can be evaluated as

$$\langle A\rangle=\langle A\rangle_0+\sum_{n=1}^{\infty}\left(\frac{1}{i\hbar}\right)^n\int_{-\infty}^{t}dt_1\int_{-\infty}^{t_1}dt_2\times\int_{-\infty}^{t_2}dt_3\cdots\int_{-\infty}^{t_{n-1}}dt_{n-1}{\rm Tr}\{A(t)H_{\rm int}(t_1)\times[H_{\rm int}(t_2)\cdots[H_{\rm int}(t_n),\rho_0]]\}, \tag{3.9}$$

where $\langle A\rangle_0$ is the average value with respect to the density matrix $\rho_0$ pertaining to the system [Eqs. (3.3) and (3.4)] unperturbed by the interaction, Eq. (3.5). The square brackets above stand for the corresponding commutators, and Tr means the trace.

If we retain only the two leading terms, Eq. (3.9) then yields

$$\langle A\rangle=\langle A\rangle_0+\frac{1}{i\hbar}\int_{-\infty}^{t}dt_1{\rm Tr}\{A(t)[H_{\rm int}(t_1),\rho_0]\}-\frac{1}{\hbar^2}\int_{-\infty}^{t}dt_1\int_{-\infty}^{dt_1}dt_2{\rm Tr}\{A(t)[H_{\rm int}(t_1),[H_{\rm int}(t_2),\rho_0]]\}. \tag{3.10}$$

Substituting $A=y_\ell$, into Eq. (3.10) gives for the average displacement at lattice site $\ell$

$$\langle y_\ell\rangle=\langle y_\ell\rangle_0+\int_{-\infty}^{\infty}dt_1\langle\langle y_\ell(t)|H_{\rm int}^{\rm op}(t_1)\rangle\rangle f(t_1)+\int_{-\infty}^{+\infty}d\tilde{\tau}_1\times\int_{-\infty}^{+\infty}d\tilde{\tau}_2\langle\langle y_\ell(0)|H_{\rm int}^{\rm op}(-\tilde{\tau}_1)\|H_{\rm int}^{\rm op}(-\tilde{\tau}_1-\tilde{\tau}_2)\rangle\rangle\times f(t-\tilde{\tau}_1)f(t-\tilde{\tau}_1-\tilde{\tau}_2)\cdots, \tag{3.11}$$

where the Green's functions have been introduced as follows:

$$\langle\langle y_\ell(0)|H_{\rm int}(-\tilde{\tau}_1)\|H_{\rm int}(-\tilde{\tau}_1-\tilde{\tau}_2)\rangle\rangle=\frac{1}{(i\hbar)^2}\theta(\tilde{\tau}_1)\theta(\tilde{\tau}_2)T_r\{y_\ell(0)\times[H_{\rm int}(-\tilde{\tau}_1),[H_{\rm int}(-\tilde{\tau}_1-\tilde{\tau}_2),\rho_0]]\}\cdots. \tag{3.12}$$

The average base-pair displacement could be rewritten following the above technique as

$$\langle y_\ell\rangle=\langle y_\ell\rangle_0+\sum_m\int_{-\infty}^{+\infty}dt_1f_m(t_1)\langle\langle y_\ell(t)|\varphi_m(t_1)\rangle\rangle+\sum_{m,n}\int_{-\infty}^{+\infty}d\tilde{\tau}_1\int_{-\infty}^{+\infty}d\tilde{\tau}_2f_m(t-\tilde{\tau}_1)f_n(t-\tilde{\tau}_1-\tilde{\tau}_2)\times\langle\langle y_\ell(0)|\varphi_m(-\tilde{\tau})\|\varphi_n(-\tilde{\tau}_1-\tilde{\tau}_2)\rangle\rangle. \tag{3.13}$$

Since the commutator $[y_\ell(t),\varphi_m(t_1)]$ equals identically zero ($[y_\ell,y_m]=0$), we conclude that only the last term in Eq. (3.11) remains to be evaluated. Let us denote it by $\langle y_\ell\rangle_{(2)}$, so we can write

$$\langle y_\ell\rangle_{(2)}=\sum_{m,n}\left(\frac{1}{2\pi}\right)^2\int_{-\infty}^{+\infty}d\omega_1\int_{-\infty}^{+\infty}d\omega_2f_m(\omega_1)f_n(\omega_2)\times\langle\langle y_\ell(0)\varphi_m\|\varphi_n\rangle\rangle e^{-it(\omega_1+\omega_2)}. \tag{3.14}$$

Starting from the identity for Green's functions

$$\langle\langle y_\ell(0)|H_{\rm int}(-\tilde{\tau}_1)\|H_{\rm int}(-\tilde{\tau}_1-\tilde{\tau}_2)\rangle\rangle=\left(\frac{1}{2\pi}\right)^2\int_{-\infty}^{+\infty}d\omega_1\int_{-\infty}^{+\infty}d\omega_2e^{i\omega_1\tilde{\tau}_1}\cdot e^{-\omega_2(\tilde{\tau}_1+\tilde{\tau}_2)}\times\langle\langle y_\ell(0)|H_{\rm int}\|H_{\rm int}\rangle\rangle_{\omega_1,\omega_2} \tag{3.15}$$

we can make the following expansion:

$$\hbar(\omega_1+\omega_2+2i\epsilon)\langle\langle y_\ell(0)|\varphi_m\|\varphi_n\rangle\rangle_{\omega_1+i\epsilon,\omega_2+i\epsilon}=\langle\langle[y_\ell,\varphi_m]|\varphi_n\rangle\rangle_{\omega_2+i\epsilon}+\langle\langle[y_\ell(0),H_0]|\varphi_m\|\varphi_n\rangle\rangle_{\omega_1+i\epsilon,\omega_2+i\epsilon}. \tag{3.16}$$

We once again remove the first term on the right-hand side of Eq. (3.16) and proceed to scrutinize the second term

$$\hbar(\omega_1+\omega_2+2i\epsilon)\langle\langle y_\ell(0)|\varphi_m\|\varphi_n\rangle\rangle_{\omega_1+i\epsilon,\omega_2+i\epsilon}=\frac{i\hbar}{M}\langle\langle P_{y\ell}|\varphi_m\|\varphi_n\rangle\rangle_{\omega_1+i\epsilon,\omega_2+i\epsilon}, \tag{3.17}$$

where we have used the commutation relation $[y_\ell, H_0] = P_{y\ell}$.

Let us proceed with expanding Eq. (3.17) as follows:

$$\begin{aligned}\hbar(\omega_1+\omega_2+2i\epsilon) &= \langle\langle P_{y\ell}|\varphi_m\|\varphi_n\rangle\rangle_{\omega_1+i\epsilon,\omega_2+i\epsilon} \\ &= \langle\langle [P_{y\ell},\varphi_m]|\varphi_n\rangle\rangle_{\omega_2+i\epsilon} \\ &\quad + \langle\langle [P_{y\ell},H_0]|\varphi_m\|\varphi_n\rangle\rangle_{\omega_1+i\epsilon,\omega_2+i\epsilon}.\end{aligned} \tag{3.18}$$

Taking into account the commutators involved, namely,

$$[P_{y\ell},\varphi_m] = -i\hbar\delta_{\ell,m}(C_\kappa + C_\kappa^+)$$

and

$$[P_{y\ell},H_0] = i\hbar\sqrt{2}aD[\exp(-2\sqrt{2}ay_\ell) - \exp(-\sqrt{2}ay_\ell)] \tag{3.19}$$

followed by the use of the decoupling of Green's functions according to

$$\begin{aligned}&\langle\langle C_\kappa + C_\kappa^\dagger|(C_\kappa + C_\kappa^\dagger)y_\ell\rangle\rangle_{\omega_2+i\epsilon} \\ &\quad = \langle y_\ell\rangle\langle\langle (C_\kappa + C_\kappa^\dagger)|(C_\kappa + C_\kappa^\dagger)\rangle\rangle_{\omega_2+i\epsilon},\end{aligned}$$

we finally obtain

$$\begin{aligned}&\hbar(\omega_1+\omega_2+2i\epsilon)\langle\langle P_{y\ell}|\varphi_m\|\varphi_n\rangle\rangle \\ &\quad = 2i\delta_{\ell,m}\frac{\Omega_\kappa}{(\omega_2+\Omega_\kappa+i\epsilon)(\omega_2-\Omega_\kappa+i\epsilon)}\langle y_\ell\rangle \\ &\qquad + i2\sqrt{2}\hbar aD\{\langle\langle[\exp(-2\sqrt{2}ay_\ell) \\ &\qquad - \exp(-\sqrt{2}ay_\ell)]|\varphi_m\|\varphi_n\rangle\rangle_{\omega_1+i\epsilon,\omega_2+i\epsilon}\},\end{aligned} \tag{3.20}$$

where $\Omega_\kappa = E_\kappa/\hbar$, with $E_\kappa$ being the energy of the amide-I excitation of the regulatory protein attached. Subsequently, we continue evaluating two commutators of exponentials with $P_{y\ell}$ and decoupling the Green's function involved, to arrive at the rather involved expression for $\langle y_\ell\rangle_{(2)}$,

$$\begin{aligned}\langle y_\ell\rangle_{(2)} &= -8\frac{(\bar{\tau})^2}{M\hbar}\sum_n \frac{1}{(2\pi)^2}\int_{-\infty}^{+\infty}d\omega_1\int_{-\infty}^{+\infty}d\omega_2 V_\ell V_n \\ &\quad \times e^{-\sigma^2(n-\ell)^2}\langle y_n\rangle_0 j_0(\tilde{\tau}\omega_1)j_0(\tilde{\tau}\omega_2) \\ &\quad \times\frac{\Omega_\kappa\exp[i\omega_1(\tilde{\tau}\ell-t)]\exp[i\omega_2(\tilde{\tau}n-t)]}{(\omega_1+\omega_2+2i\epsilon)^2(\omega_2+\Omega_k+i\epsilon)(\omega_2-\Omega_\kappa+i\epsilon)} \\ &\quad \times\left\{1+\frac{8\frac{a^2D}{M}\langle\exp(-2\sqrt{2}ay_\ell)\rangle_0}{(\omega_1+\omega_2+2i\epsilon)\left(\omega_1+\omega_2+\frac{4\hbar a^2}{M}+2i\epsilon\right)}\right. \\ &\quad \left. -\frac{4\frac{a^2D}{M}\langle\exp(-\sqrt{2}ay_\ell)\rangle_0}{(\omega_1+\omega_2+2i\epsilon)\left(\omega_1+\omega_2+\frac{\hbar a^2}{M}+2i\epsilon\right)}\right\},\end{aligned} \tag{3.21}$$

where $j_0(x) = \sin x/x$ represents the zeroth order Bessel function. The only task still remaining is the integration with respect to $\omega_1$ and $\omega_2$. This is accomplished through fairly cumbersome calculations of Cauchy integrals, which eventually yield an elegantly symmetric but large expression for the average base-pairs displacement impacted by a regulatory protein attached to the DNA chain,

$$\begin{aligned}\langle y_\ell\rangle &= \langle y_\ell\rangle_0 + \sum_n V_\ell V_n\langle y_n\rangle_0 e^{-\sigma(n-\ell)^2}8\frac{(\tilde{\tau})^2}{M\hbar}j_0(\tilde{\tau}\Omega_\kappa)\left\{\tilde{\tau}\cdot j_1(\tilde{\tau}\Omega_\kappa)\cos[\Omega_\kappa\tilde{\tau}(n-\ell)]\right. \\ &\quad -(\tilde{\tau}\ell-t)j_0(\tilde{\tau}\Omega_\kappa)\sin[\Omega_\kappa\tilde{\tau}(n-\ell)] + 2\frac{a^2D}{M}\left[\{\tilde{\tau}(\tilde{\tau}-t)j_1(\tilde{\tau}\Omega_\kappa)\sin[\Omega_\kappa\tilde{\tau}(n-\ell)] - \tfrac{1}{2}(\tilde{\tau})^2 j_2(\tilde{\tau}\Omega_\kappa)\right. \\ &\quad \times\cos[\Omega_\kappa\tilde{\tau}(n-\ell)] + \tfrac{1}{2}(\tilde{\tau}-t)^2 j_0(\tilde{\tau}-\Omega_\kappa)\cos[\Omega_\kappa\tilde{\tau}(n-\ell)]\}\frac{4}{\omega_M}[\langle\exp(-2\sqrt{2}ay_\ell)\rangle_0 - 2\langle\exp(-\sqrt{2}ay_\ell)\rangle_0] \\ &\quad + j_0(\tilde{\tau}\Omega_\kappa)\cos[\Omega_\kappa\tilde{\tau}(n-\ell)]\frac{4}{\omega_M^3}[\langle\exp(-2\sqrt{2}ay_\ell)\rangle_0 - 32\langle\exp(-\sqrt{2}ay_\ell)\rangle_0] - \frac{1}{\omega_M^3}\left(2\langle\exp(-2\sqrt{2}ay_\ell)\rangle_0\right. \\ &\quad \times\{j_0(\tilde{\tau}[\Omega_\kappa+\omega_M])\cos[\Omega_\kappa\tilde{\tau}(n-\ell)-\omega_M(\tilde{\tau}_\ell-t)] + j_0(\tilde{\tau}[\Omega_\kappa-\omega_M])\cos[\Omega_\kappa\tilde{\tau}(n-\ell)+\omega_M(\tilde{\tau}\ell-t)]\} \\ &\quad -64\langle\exp(-\sqrt{2}ay_\ell)\rangle_0\left\{j_0\left(\tilde{\tau}\left[\Omega_\kappa+\frac{\omega_M}{4}\right]\right)\cos\left[\Omega_\kappa\tilde{\tau}(n-\ell)-\frac{\omega_M}{4}(\tilde{\tau}\ell-t)\right]\right. \\ &\quad \left.\left.\left.\left.+j_0\left(\tilde{\tau}\left[\Omega_\kappa-\frac{\omega_M}{4}\right]\right)\cos\left[\Omega_\kappa\tilde{\tau}(n-\ell)+\frac{\omega_M}{4}(\tilde{\tau}\ell-t)\right]\right\}\right)\right\}.\end{aligned} \tag{3.22}$$

Here the new characteristic frequency $\omega_M$ represents

$$\omega_M = \frac{4\hbar a^2}{M}, \tag{3.23}$$

and $j_1(x)$ and $j_2(x)$ stand for the corresponding Bessel functions. Note that the notation $\langle\cdots\rangle_0$ indicates an average value with respect to the density matrix $\rho_0$ of the unperturbed system, Eq. (3.2).

The rather complex expression in Eq. (3.22) will now be significantly simplified due to the fact that the impact of protein on the base-pair displacements is greatest with respect to the coupled base pair. Consequently we may put $n=\ell$ and $t=\tilde{\tau}\ell$, thus yielding

$$\langle y_\ell(\tilde{\tau}\ell)\rangle=\langle y_\ell\rangle_0+8\frac{(\tilde{\tau})^2}{M\hbar}V_\ell^2\langle y_\ell\rangle_0 j_0(\tilde{\tau}\Omega_\kappa)\Bigg(\tilde{\tau}j_1(\tilde{\tau}\Omega_\kappa)+2\frac{a^2D}{M}\Bigg\{-\tfrac{1}{2}(\tilde{\tau})^2 j_0(\tilde{\tau}\Omega_\kappa)\frac{4}{\omega_M}[\langle\exp(-2\sqrt{2}ay_\ell)\rangle_0$$
$$-2\langle\exp(-\sqrt{2}ay_\ell)\rangle_0]+j_0(\tilde{\tau}\Omega_\kappa)\frac{4}{\omega_M^3}[\langle\exp(-2\sqrt{2}ay_\ell)\rangle_0-32\langle\exp(-\sqrt{2}ay_\ell)\rangle_0]-\frac{1}{\omega_M^3}\Bigg[2\langle\exp(-\sqrt{2}ay_\ell)\rangle_0$$
$$\times\{j_0(\tilde{\tau}[\Omega_\kappa+\omega_M])+j_0(\tilde{\tau}[\Omega_\kappa-\omega_M])\}-64\langle\exp(-\sqrt{2}ay_\ell)\rangle_0\Bigg\{j_0\Bigg(\tilde{\tau}\Bigg[\Omega_\kappa+\frac{\omega_M}{\hbar}\Bigg]\Bigg)+j_0\Bigg(\tilde{\tau}\Bigg[\Omega_\kappa-\frac{\omega_M}{\hbar}\Bigg]\Bigg)\Bigg\}\Bigg]\Bigg\}\Bigg). \tag{3.24}$$

Substituting the parameter values $a$ and $M$ from Eq. (2.23) and using the definition of $\omega_M$, Eq. (3.23), leads to the following estimate:

$$\omega_M=3.10^{11}\ \text{rad/s}. \tag{3.25}$$

Therefore, the expression (3.22) could be further simplified discarding the terms proportional to $\omega_M^{-3}$, and eventually yielding a manageable formula

$$\langle y_\ell(\tilde{\tau})\rangle=\langle y_\ell\rangle_0\Bigg\{1+\frac{8V_\ell\tilde{\tau}^3}{M\hbar}j_0(\tilde{\tau}\Omega_\kappa)j_1(\tilde{\tau}\Omega_\kappa)$$
$$+\frac{8V_\ell^2D\tilde{\tau}^4}{M\hbar^2}j_0^2(\tilde{\tau}\Omega_\kappa)[2\langle\exp(-2\sqrt{2}ay_\ell)\rangle_0$$
$$-\langle\exp(-\sqrt{2}ay_\ell)\rangle_0]\Bigg\}. \tag{3.26}$$

In order to estimate and discuss the numerical value of Eq. (3.26), we first focus on the equilibrium average displacement of base pairs $\langle y\rangle_0$ without the impact of regulatory proteins. The corresponding statistics was examined earlier by other authors for the case of thermal fluctuations in a DNA chain [24] and then extended later by one of the present authors for the case where the intrinsic electromagnetic fields play a catalytic role in the breather's dynamics [25]. In the case of thermal excitations it was estimated that the average base-pair stretching at physiological temperatures is of the order

$$\langle y_\ell\rangle_0\simeq 1\times10^{-11}\ \text{m}, \tag{3.27}$$

while in the case of strong intrinsic ac fields [25] the value increases by up to another order of magnitude so that

$$\langle y_\ell\rangle_0^{AC}\simeq 1\times10^{-10}\ \text{m}, \tag{3.28}$$

enabling the appearance of the so-called fluctuational openings in the DNA chain. If we use $\Omega_\kappa$ from Eq. (3.4) and take the interaction time $\tilde{\tau}$ as equal to the amide-I mode lifetime putting $\tilde{\tau}=10^{-12}$ s, we obtain

$$\tilde{\tau}\Omega_\kappa\simeq 3\times10^2. \tag{3.29}$$

Therefore, this large value of the argument allows us to take into account the asymptotic behavior of the Bessel functions involved, i.e.,

$$j_0(\tilde{\tau}\Omega_\kappa)\simeq\frac{\sin(\tilde{\tau}\Omega_\kappa)}{\tilde{\tau}\Omega_\kappa};\quad j_1(\tilde{\tau}\Omega_\kappa)\simeq\frac{\sin\left(\tilde{\tau}\Omega_\kappa-\frac{\pi}{2}\right)}{\tilde{\tau}\Omega_\kappa}, \tag{3.30}$$

which transforms Eq. (3.26) into the more transparent form given below

$$\langle y_\ell(\tilde{\tau})\rangle=\langle y_\ell\rangle_0\Bigg\{1-\frac{4V_\ell^2\tilde{\tau}}{M\hbar\Omega_k^2}\sin[2(\tilde{\tau}\Omega_\kappa)]$$
$$+\frac{8V_\ell^2D\tilde{\tau}^2}{M\hbar^2\Omega_\kappa^2}\sin^2(\tilde{\tau}\Omega_\kappa)[2\langle\exp(-2\sqrt{2}ay_\ell)\rangle_0$$
$$-\langle\exp(-\sqrt{2}ay_\ell)\rangle_0]\Bigg\}. \tag{3.31}$$

From Ref. [26] it follows that the average force of the hydrogen bonds in DNA base complexes is in the range of about $3\times10^{-10}$ N. This force could be attributed to the hydrogen-bridged interaction term $V_\ell$ in Eq. (3.31). Taking the value $M=5.4\times10^{-24}$ kg, we estimate that the second term in the curly brackets of Eq. (3.31) is on the order of

$$\frac{4V_\ell^2\tilde{\tau}}{M\hbar\Omega_\kappa^2}\leqslant 10^{-2}. \tag{3.32}$$

Let us finally estimate the third term including the nonlinear Morse potential in the model we have developed here. In addition to the value adopted above, we take into account $D=0.1$ eV and $y_\ell\simeq10^{-11}$ m yielding

$$\frac{8V_\ell^2 D\tilde{\tau}^2}{M\hbar^2\Omega_\kappa^2}\sin^2(\tilde{\tau}\Omega_\kappa)[2\langle\exp(-2\sqrt{2}ay_\ell)\rangle_0 - \langle\exp(-\sqrt{2}ay_\ell)\rangle_0] \simeq 2.5\sin^2(\tilde{\tau}\Omega_\kappa). \quad (3.33)$$

Note that the expression in Eq. (3.33) is highly sensitive to the value $(\tau\Omega_\kappa)$ that reveals resonant character of the process for

$$\sin(\tau\Omega_\kappa)\to 1. \quad (3.34)$$

We infer, therefore, that the regulatory proteins would similarly increase the breathers amplitude.

## IV. CONCLUSIONS AND DISCUSSION

In this paper we have considered an application of the Peyrard-Bishop model in our extended version to the nonlinear dynamics of DNA in the presence of regulatory proteins. Our initial thrust was directed towards specifying the model parameters for the case of the DNA double helix. While there still remains a certain amount of ambiguity regarding the numerical values that should be adopted for DNA, we have tried to make our numerical value selections as safe as possible. It has been concluded through our analysis that a breather solution is likely to be generated spontaneously or by external means, such as protein-DNA interactions or ATP hydrolysis effects. We have investigated the possibility of long-range breather propagation as a result of the protein-DNA binding. The motivation for this effort was given by a number of empirical studies showing a rather intriguing long-range interaction effect of one protein binding site on another along the DNA chain. The application of the PB model to this case involved an addition of the amide-I mode to the DNA Hamiltonian and its interaction with DNA base pairs. In order to evaluate realistic effects at physiological temperatures we have subsequently calculated nonequilibrium thermodynamic averages of the displacement coordinates. The key finding in this study is that both the spatial and temporal characteristics of the localized solution can be significantly extended by protein-DNA interaction. Furthermore, the nature of the system's response is strongly resonant offering a glimpse into the high levels of specificity involved in the DNA functioning. We hope that this latter finding can be supported by future experimental results regarding DNA-protein interactions.

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